Review Neurochem Int. 2016 Oct:99:110-132. doi: 10.1016/j.neuint.2016.06.011.
Epub 2016 Jun 23.

The neuropharmacology of butyrate: The bread and butter of the microbiota-gut-brain axis?

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PMID: 27346602 DOI: 10.1016/j.neuint.2016.06.011

Abstract

Several lines of evidence suggest that brain function and behaviour are influenced by microbial metabolites. Key products of the microbiota are short-chain fatty acids (SCFAs), including butyric acid. Butyrate is a functionally versatile molecule that is produced in the mammalian gut by fermentation of dietary fibre and is enriched in butter and other dairy products. Butyrate along with other fermentation-derived SCFAs (e.g. acetate, propionate) and the structurally related ketone bodies (e.g. acetoacetate and d-β-hydroxybutyrate) show promising effects in various diseases including obesity, diabetes, inflammatory (bowel) diseases, and colorectal cancer as well as neurological disorders. Indeed, it is clear that host energy metabolism and immune functions critically depend on butyrate as a potent regulator, highlighting butyrate as a key mediator of host-microbe crosstalk. In addition to specific receptors (GPR43/FFAR2; GPR41/FFAR3; GPR109a/HCAR2) and transporters (MCT1/SLC16A1; SMCT1/SLC5A8), its effects are mediated by utilisation as an energy source via the β-oxidation pathway and as an inhibitor of histone deacetylases (HDACs), promoting histone acetylation and stimulation of gene expression in host cells. The latter has also led to the use of butyrate as an experimental drug in models for neurological disorders ranging from depression to neurodegenerative diseases and cognitive impairment. Here we provide a critical review of the literature on butyrate and its effects on multiple aspects of host physiology with a focus on brain function and behaviour. We find fundamental differences in natural butyrate at physiological concentrations and its use as a neuropharmacological agent at rather high, supraphysiological doses in brain research. Finally, we hypothesise that butyrate and other volatile SCFAs produced by microbes may be involved in regulating the impact of the microbiome on behaviour including social communication.

Keywords: Endocrine; Gut-brain axis; Neuroepigenetics; Nutrition; Sociability; Treg.

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